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	Title: "T CELL REGULATORY GENES ASSOCIATED WITH IMMUNE DISEASE"	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated October 29, 2008. No claims have been allowed. Claims 1, 4, 7, 8, and 20-23 are pending. Claims 5, 6, and 9-19 are canceled. The rejection of Claims 1, 4, 7, 8, and 20-23 is appealed. A Notice of Appeal was filed on February 12, 2009. The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134(a).

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. STAN-235CIP to cover any required fee for filing the Applicant's brief. Additionally, in the event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, the Appellant petitions for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to the above disclosed deposit account.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real parties in interest are the Board of Trustees of the Leland Stanford Junior University, by virtue of the assignment recorded reel and frame 017038/0220 and the Dana-Farber Cancer Instituted, Inc., by virtue of the assignment recorded reel and frame 017038/0218.

II. RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

III. STATUS OF CLAIMS

The present application was filed on September 15, 2003 with Claims 1-19. During the course of prosecution, Claims 5, 6, and 9-19 were canceled, Claims 2 and 3 were withdrawn and Claims 20-23 were added. Accordingly, Claims 1, 4, 7, 8, and 20-23 are pending and under review in the present application, all of which stand rejected and are appealed herein.

IV. STATUS OF AMENDMENTS

Claims 4 and 6 were amended, Claims 10-19 were canceled, and Claims 2-3 and 5-6 were withdrawn in the Response mailed July 13, 2006, and the amendments were entered as noted in the Office Action mailed September 1, 2006. Claims 1 and 8 were amended, Claim 9 was canceled, and Claims 20-23 were added in the Response mailed December 20, 2006 and Claim 4 was amended in the Response mailed March 22, 2007, which amendments entered as noted in the Final Office Action mailed October 4, 2007. Claims 1, 4, 8, 20, and 23 were amended in the Response to accompany RCE mailed October 31, 2007, and the amendments entered as noted in the Office Action mailed March 5, 2008. Claim 23 was amended in a Response mailed on August 5, 2008, and the amendments entered as noted in the Final Office Action mailed October 29, 2008. No further amendments have been made to the claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method for screening for an individual's predisposition to atopy.

Claim 1 is drawn to a method for screening for an individual's predisposition to atopy, the method comprising analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample comprising DNA or mRNA from said individual with probes that specifically bind under stringent conditions to nucleic acid sequences of a TIM-1 gene (page 2, lines 25-27; page 15, lines 1-5), wherein the presence of said polymorphism is indicative of an individual's predisposition to develop said atopy (page 2, lines 25-27).

Claim 8 is drawn to a method for screening for an individual's predisposition to atopy, the method comprising analyzing the individual for the presence of an INS157 polymorphism in TIM-1 by contacting a biological sample comprising DNA or mRNA from such individual with a probe that specifically binds to the nucleic acid sequence ATGACAACGACTGTTCCA, SEQ ID NO:22, bases 472-489, encoding the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 (page 10, lines27-31; page 13, lines 6-7); detecting the presence of a complex formed between the probe and the genomic DNA, mRNA or a transcript thereof; and analyzing the individual for the presence of hepatitis A virus (HAV) seropositivity (page 13, lines 7-8), wherein the seropositivity in an individual comprising an allele of TIM-1 comprising the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 is indicative of a reduced risk of developing atopy (page 2, lines 25-27; page 13, lines 11-14).

Claim 20 is drawn to a method of screening for a human individual's predisposition to atopy, the method comprising analyzing the individual for the presence of an INS157 polymorphism in TIM-1 by contacting a biological sample comprising DNA or mRNA from the individual with a probe that specifically binds to a nucleic acid sequence encoding the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 (page 10, lines27-31; page 13, lines 6-7), wherein the presence of the INS157 polymorphism is indicative of an individual's predisposition to develop the atopy (page 2, lines 25-27).

Claim 23 is drawn to a method of screening for a human individual's predisposition to atopy, the method comprising analyzing the individual for the presence of at least one TIM-1 polymorphism in exon 3 by contacting a biological sample comprising DNA or mRNA from the individual with probes that specifically bind under stringent conditions to nucleic acid sequences in exon 3 of a TIM-1 gene (page 9, lines 4-7), wherein the presence of the polymorphism is indicative of an individual's predisposition to develop the atopy (page 2, lines 25-27).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are 2 grounds for rejection of the claims:

I. Claims 1, 4, 7-8 and 20-23 have been rejected under 35 U.S.C. 112, first paragraph. It is stated that the specification, while being enabling for a method for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of 157insMTTTVP (polymorphism 1, SEQ ID NO:22), of TIM-1 in hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to protects against atopy, does not reasonably provide enablement for a method for screening for a human individual's predisposition to any atopy by analyzing for the presence of any TIM-1 polymorphism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

II. Claims 1, 4, 7 and 23 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. It is stated that the claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

VII. ARGUMENT

I. Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement for the full scope of the claimed invention.

With respect to enablement, courts have held that: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

To comply with 35 U.S.C. § 112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue". As reviewed by the Office in the Office Action of March 5, 2008 and the Final Office Action of October 29, 2008, one way to determine if undue

experimentation is required is to analyze the subject specification in light of the *Wands* factors:[1] (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the quantity of experimentation necessary, (6) the relative skill of those in the art, (7) the amount of direction or guidance presented, and (8) the presence or absence of working examples. However, all of the factors need not be reviewed when determining whether a disclosure is enabling.[2]

Grouping of claims. Independent Claim 1 states a method of screening for a human individual's predisposition to atopy by analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample comprising DNA or mRNA from the individual with probes that specifically bind under stringent conditions to nucleic acid sequences of a TIM-1 gene, where the presence of the polymorphism is indicative of an individual's predisposition to develop atopy. Independent Claim 8 specifically refers to detection of the INS57 polymorphism in Tim-1 and analyzing an individual for the presence of HAV seropositivity. Claim 20 specifically refers to detection of the INS157 polymorphism in TIM-1, and Claim 23 to detection of polymorphisms in exon 3 of Tim-1. For purposes of enablement and written description, the recitation of a specific mutation in Claims 8 and 20 and the claims that depend thereupon set the claims apart from Claims 1 and 23 and the claims that depend thereupon, and it is appropriate to consider the patentability of these two groups separately.

The Office acknowledges that the specification is enabling for a method for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of 157insMTTTVP (polymorphism 1, SEQ ID NO:22), of TIM-1 in hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to protects against atopy. However, it is asserted that the specification does not provide enablement for methods for screening for a human individual's predisposition to any atopy by analyzing for the presence of any TIM-1 polymorphism. In establishing this rejection, the Office reviews the pending claims in light of the *Wands* factors.

The Appellants submit that, when evaluated in view of the relevant *Wands* factors, the specification does, in fact, clearly enable one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 1, 4, 7-8 and 20-23 recite subject matter that is adequately described in the specification in view of the art in such a way that one of ordinary skill in the art would be able to make and use the claimed invention without having to practice undue

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[1] *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)

[2] See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991)

experimentation. The relevant enablement factors cited in the Office Action are discussed in detail below.

The nature of the invention and the breadth of the claims

The claims are drawn to a method of screening for a human individual's predisposition to atopy by analyzing the presence of at least one TIM-1 polymorphism where the presence of the polymorphism is indicative of individual's predisposition to develop atopy. The claims are further drawn to a method of contacting a biological sample with a probe that specifically binds to nucleic acid sequences of a TIM-1 gene (Claim 1), nucleic acid sequences encoding the SEQ ID NO:22 encoding the 157insMTTTVP polymorphism of TIM-1 (Claims 8 and 20), or nucleic acid acids in exon 3 of TIM-1 (Claim 23) or with probes that specifically bind to polymorphisms in exon 3 of TIM-1 gene and which may further comprising a step of analyzing an individual for presence of Hepatitis A virus seropositivity (Claim 8).

With regard to the nature of the invention and the breadth of the claims, the Final Office Action of October 4, 2007 asserted that "The rejected claims encompass any type of atopy and detection of any polymorphism in TIM-1. The nature of the invention requires knowledge of a correlation between detection of the presence of a TIM-1 polymorphism and predisposition to develop atopy." (page 6, line 1-4)

Appellants submitted in their response of October 31, 2007 that the claims encompass screening for a human individual's predisposition to atopy by analyzing the individual for the presence of polymorphisms in TIM-1 gene, where the presence of the polymorphism is indicative of the individual's predisposition to develop atopy. The claims do not encompass correlating the presence of a polymorphism to the development of atopy but rather the claims encompass presence of a polymorphism being indicative of the individual's predisposition to develop atopy. For example claim 20 recites detecting a common TIM-1 polymorphism, 157insMTTTVP, and associating its presence to the individual's predisposition to develop atopic disorder. Appellants are not claiming that every polymorphism in TIM-1 is related to atopy. The Appellants are limiting their claims to method of detecting polymorphisms in TIM-1, which information is useful to an individual wishing to evaluate their predisposition to atopy, and which information may be further evaluated in the context of HAV-1 seropositivity.

Furthermore, atopy is a distinct medical condition. The art recognizes atopic immunological disorder or atopy as an allergic hypersensitivity affecting parts of the body not in direct contact with the allergen. It includes eczema (atopic dermatitis), allergic conjunctivitis, allergic rhinitis and asthma. Atopy is a well characterised medical condition with underlying immune dysfunction which

manifests in specific clinical phenomenon. The art refers to this condition in multiple references provided herein.

Furthermore, the Appellants submitted that both the specification and the art teach a correlation between TIM-1 polymorphisms and atopy. A description of common polymorphisms in TIM-1 and the linkage of TIM-1 locus to development of atopy can be found in the specification on e.g., Page 8, paragraph 37-43; page 13, paragraph 51; page 46, paragraph 169-175 and page 53, paragraph 192-200. It is shown in the instant specification that information regarding an individual's predisposition to atopy is obtained from analysis of polymorphisms in TIM-1.

Moreover, the art provides numerous publications that corroborate the correlation between detection of the presence of a TIM-1 polymorphism and predisposition to atopy. For example, Sizing et al. in J. Immunol. 2007 Feb 15; 178(4):2249-61 describe using monoclonal antibodies against TIM-1 to show that TIM-1 influences the extent of lung inflammation. Graves et al. in J Allergy Clin Immunol. 2005 Sep; 116(3):650-6 report a 15-bp insertion/deletion in exon4 of TIM1 being significantly related to atopy.

In response to the Appellants' first point, the Office Action filed March 5, 2008 asserted that claims are not limited to a method of detecting a polymorphism in TIM-1 gene, but rather that the claims are drawn to a method of screening an individuals predisposition to atopy by analyzing the presence of the TIM-1 polymorphism. The Office asserted that the claims require the presence of a polymorphism that is indicative of atopy. The Office maintained that the claims require that there is a correlation between the presence of a polymorphism in TIM- 1 gene and atopy, be it development of atopy, predisposition to atopy, etc. The Office asserted that the claims are not limited to specific polymorphisms and recite at least one polymorphism in TIM- 1 and therefore broadly encompass any polymorphism in the TIM-1 gene.

With regard to the Appellants' second point that the specification teaches 7 polymorphisms (paragraph 37), the March 5, 2008 Office Action asserted that the specification does not teach an association between these 7 polymorphisms and atopy, but rather, that the specification only provides a predictable association between HAV (+) and 157insMTTTVP polymorphism in a Caucasian population. The Office asserted that the specification does not provide any analysis of representative number of polymorphisms with atopy other than 157insMTTTVP.

With regard to the Appellant's third point that numerous publication have corroborated the correlation between the detection of the presence of TIM-1 polymorphism and predisposition to atopy, the March 5, 2008 Office Action noted that the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. The Office asserted that the publications relied upon by Appellants are post filing publications and are

therefore not evidence of the state of the art at the time of filing. With respect to the individual references relied upon by applicant, the Office asserted that Graves et al. teach that their findings need to be replicated in other studies (See pg. 655, 2nd column, last para). Furthermore, the Office asserted that Graves et al. analyze only one polymorphism within TIM-1 a 15bp insertion (see pg. 655, lst column, lst full para), which is not disclosed in the present specification. Additionally, the Office asserted that Sizing et al. teach that in 2007 the TIM-1 locus was linked to atopic disease (see abstract), and that Sizing et al. does not teach analysis of polymorphisms within TIM-1 gene and atopy in humans, as Sizing et al.'s analysis was demonstrated in mice not humans (See pg. 2251). Therefore, the Office concluded, Sizing et al. cannot be relied upon to corroborate the correlation between the presence of TIM-1 polymorphisms and predisposition to atopy in humans at the time of filing.

Appellants maintain herein that they are not claiming that every polymorphism in TIM-1 is related to atopy, but rather that the claims are limited to method of detecting polymorphisms in TIM-1, which information is useful to an individual wishing to evaluate their predisposition to atopy, and which information may be further evaluated in the context of HAV-1 seropositivity. They maintain that atopy is a well characterised medical condition with underlying immune dysfunction which manifests in specific clinical phenomenon, and thus, that with regard to the element of "a method of screening for a human individual's predispositon to atopy", the pending claims are not unduly broad. Furthermore, the Appellants maintain that both the specification and the art teach a correlation between TIM-1 polymorphisms and atopy, be it in humans or mouse models of human disease, and thus, that with regard to the element of "analyzing said individual for the presence of at least one TIM-1 polymorphism . . . wherein the presence of said polymorphism is indicative of individual's predisposition to develop atopy", the pending claims are also not unduly broad.

Accordingly, the Appellants maintain that the nature of the invention is not complex, and the claims are not unduly broad.

Guidance in the specification and working examples

With regard to the guidance and working examples provided by the specification, the Final Office Action of October 4, 2007 asserted that "Although determination of allele is routine in the art, predictably correlating an allele to atopy in any human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with atopy in any human individual." (page 6, line 22 – page 7, line 3)

Appellants disagreed in their response of October 31, 2007, submitting that the claims do not recite that every polymorphism in TIM-1 is related to an atopic disorder. The claims are limited to

detecting polymorphisms in TIM-1 gene, which information is useful to an individual wishing to evaluate their predisposition to atopy, and which information may be further evaluated in the context of HAV-1 seropositivity.

Moreover, MPEP 2138.05 states that reduction to practice may be an actual reduction or a constructive reduction to practice. The instant specification shows, in multiple experimental examples, unambiguous evidence that the TIM-1 gene is associated with atopy. The constructive reduction to practice constituted by the present application thus provides both a rationale for the selection of the TIM-1 gene as a screening tool for predisposition to atopic disorders and the means to effect such screening using TIM-1 alleles in individuals. Accordingly, the specification amply supports a constructive reduction to practice for the claimed genus of TIM-1 alleles.

Furthermore, the instant specification provides atopic conditions of interest to the claimed method, a detailed description of the TIM gene family including its chromosomal location and sequence content, molecular characteristics of the TIM gene products including sequence motifs and structural features, numerous referenced publications linking the TIM gene family to multiple atopic disorders, description of the important role of the TIM-1 gene in immunological responses, methods of isolating TIM genes from tissue samples, techniques for genotyping TIM alleles for the purpose of diagnosis, and typical methods of preparing and detecting probes. Thus, the specification provides suitable guidance such that the ordinarily skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and use such polymorphisms for diagnostic purposes by employing straightforward techniques known to the art.

In response to the Appellants' first point, the Office Action filed March 5, 2008 agreed that the claims do not recite that every polymorphism in TIM-1 is related to atopic disorder; however, the Office asserted, the claims encompass any TIM-1 polymorphism is associated with atopy. The Office asserted that the specification does not disclose a representative number of polymorphisms predictably associated with atopy. Furthermore, that the claims are not limited to a method of detecting polymorphisms in TIM-1 gene, the claims are drawn to a method of screening for a human's individual predisposition to atopy and therefore the claims encompass the analysis that a TIM- 1 polymorphism is predictably associated with atopy. (page 18, line 12-22)

With regard to the Appellants' second point that constructive reduction to practice constituted by the present application provides a rationale for the selection of the TIM- 1 gene as a screening tool for atopic disorders and means to effect such screening, the March 5, 2008 Office Action noted that the claims are not limited to a method of screening for a TIM-1 gene; rather, that the claims require the knowledge that a specific polymorphism is associated with atopy. The Office asserted that the specification does not teach a representative number of polymorphisms associated with

atopy. Furthermore, the Office asserted that the association of the TIM-1 gene with atopy does not provide a reduction to practice for polymorphisms within the TIM- 1 gene. The Office asserted that the post filing art teaches that even if a gene is associated with involvement of a disorder does not reason that a polymorphism within the gene with also be associated with a disorder (See Hattersly and Hegele above). (page 19, line 1-11)

With regard to the Appellants' second point that the specification provides everything that is needed such that the ordinary skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and use such polymorphisms for diagnostic purposes, the March 5, 2008 Office Action asserted that proof of constructive reduction to practice requires sufficient disclosure under 35 USC 112, 1st paragraph, how to use and how to make, but that in the instant case, the specification does not provide sufficient disclosure for a representative number of polymorphisms within the TIM- 1 gene and their association to atopy disorder. Furthermore, the Office asserted that although the specification does disclose molecular characteristic of the TIM-1 gene and TIM gene family, this does not teach how to make and use the claimed invention. The Office provided the example that the specification does not disclose a representative number of alleles within the TIM-1 gene that are predictably associated with atopy. The Office asserted that as taught by the post filing art, SNP association is unpredictable and requires large sample sizes and analysis of each polymorphism, and that, as such, the specification is not enable for any polymorphism within the TIM-1 gene to be predictably associated with atopy and therefore the specification does not provide proof of constructive reduction to practice. The Office maintained that while identifying polymorphic allelic variants of a gene is routine in the art, the ability to predictably correlate the polymorphic variants with a disease is unpredictable. The Office asserted that in the instant case, the specification is suggesting the role of TIM-1 in immunological response and atopic disease and suggesting that polymorphisms within this gene may be associated with an atopic disease; however, the specification does not provide evidence that polymorphisms within TIM- 1 gene in any population are associated with atopic disease. The Office asserted that the specification asserts an association of one polymorphism with the TIM-1 gene with protection against atopy; however, the specification does not demonstrate the presence of a polymorphism within the TIM-1 gene and predisposition to developing atopy. (page 19, line 12 – page 20, line 19)

The Appellants maintain herein that, as discussed in their October 31, 2007 response, the specification provides multiple experimental examples of an association of TIM-1 gene polymorphisms with atopy. Further, that the art also provides multiple working examples of how TIM polymorphisms are associated with atopy. Finally, that the specification provides ample guidance by providing atopic conditions of interest to the claimed method, a detailed description of the TIM gene

family including its chromosomal location and sequence content, molecular characteristics of the TIM gene products including sequence motifs and structural features, numerous referenced publications linking the TIM gene family to multiple atopic disorders, description of the important role of the TIM-1 gene in immunological responses, methods of isolating TIM genes from tissue samples, techniques for genotyping TIM alleles for the purpose of diagnosis, and typical methods of preparing and detecting probes. Accordingly, that the specification in view of the art provides suitable working examples and guidance to support the pending claim element "analyzing said individual for the presence of at least one TIM-1 polymorphism . . . wherein the presence of said polymorphism is indicative of individual's predisposition to develop atopy."

With regard to the guidance and working examples provided by the specification, the Final Office Action of October 4, 2007 also asserted that "Although table 1 of the specification demonstrates that HAV positive subjects with the 157insMTTTVP TIM-1 allele are associated with protection against atopy, tables S3 and S4 demonstrate that 157insMTTTVP is predictably correlative for only the Caucasian population that is HAV positive and that are homozygous for 157insMTTTVP allele". Further, that "Table S4 demonstrates that neither the HAV negative nor HAV positive population of Asian subjects is statistically relevant to diagnose a predisposition to any immunological disorder or atopy and table S3 demonstrates that the only statistically relevant data in the Caucasian subjects is for Caucasian subjects with HAV that are homozygous for 157insMTTTVP allele. The specification asserts that the African American sample size was too small to present separately." (page 7, line 14-page 8, line 2)

Appellants submitted in their response of October 31, 2007 that this is incorrect. In both tables, consisting of subgroup analyses for Caucasian and Asian populations, the "157insMTTTVP 1,2 vs 0 alleles" column reports a significant P value for HAV+ individuals, P=0.024 (odds = 0.105-0.870) and P=0.036 (odds=0.070-0.897), respectively. As such, the 157insMTTTVP allele is predictably correlative for the group including seropositive heterozygous and homozygous individuals in both Caucasian and Asian populations. It is unclear why the Office Action states that this is not "statistically relevant" data.

The Appellants further submitted that the lack of presentation of a subgroup analysis of African American individuals is due solely to the small n value of the group (specification, paragraph 202). Since the analysis according to Table 1 was performed using a Cochran-Mantel-Haenszel chi-square test with racial stratification (specification, paragraph 199), the statistical conclusion therein is valid for all included ethnicities.

With regard to the Appellants' first point that, statistically speaking, 157insMTTTVP is predictably correlative for the group including seropositive heterozygous and homozygous individuals, the Office Action filed March 5, 2008 asserted that the column 1, 2 vs 0 allele is for "1 or 2 copies" of 157insMTTTVP polymorphism, column 2 vs 0 allele is analysis of 2 copies of the polymorphism (homozygous), and the column 1 vs 0 allele is analysis of one copy of the polymorphism (heterozygous). Thus, the Office maintained, table S4 demonstrates that analysis based solely on either heterozygosity or homozygosity (one or two copies) 157insMTTTVP is not predictably associated with atopy in HAV + in the Asian population. The Office asserted that it is unclear how column 1, 2 vs 0 allele is statistically significant when the analysis of the one copy or two copy alone does not provide statistically significant data, hence the conclusion of the examiner that the data in table S4 is not statistically significant as it appears that column 1, 2 vs 0 allele is the combination of the other two columns within table S4 and its unclear how this column has a p value that is .036 while the other two analyses have a p value of .096 and .113. (page 21, line 1-12)

With regard to the Appellants' second point that the lack of presentation of a subgroup analysis of African American individuals is due solely to the small n value of the group, the March 5, 2008 Office Action asserted that the specification provides evidence that 157insMTTTVP allele is not predictably associated with atopy in either Caucasians or Asians, much less African Americans and provides no evidence of other polymorphisms associated with atopy. Thus, the Office concluded, the specification demonstrates that confirming the finding of an association of a polymorphism with a disorder will not necessarily be confirmed in subpopulations and demonstrates the unpredictability of associating the presence of any polymorphism within the TIM- 1 gene to predisposition to develop atopic immunological disorder. (page 21, line 13 – page 22, line 2)

In response, the Appellants submitted in their response of August 5, 2008 that the statistical analysis of Applicant's data presented in the working examples of the instant application and the conclusions of the statistical analysis was published in a premier peer reviewed journal, Nature (McIntire et al. Nature (2003) vol. 425, p. 576), where before being selected for publication, the data and the conclusions were examined by experts in the field. The Appellants submit that they have proven the validity of their statistical analysis by publishing in the esteemed journal the same data being challenged by the Office.

In response, the Final Office Action of October 29, 2008 agreed that the specification has provided statistical analysis for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of 157insMTTFR (polymorphism 1, SEQ ID No. 22), of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the 157insMTTTW insertion is indicative of a Caucasian's predisposition to protect

against atopy, but maintained that neither the post filing art or published art in Nature predictably correlate nor provide statistical analysis that provide an association of a representative number of polymorphisms in the TIM-1 gene with atopy in a human. The Office further asserted that McIntire et al. teach that only in individuals that have the 157insMTTTVP variant and are HAV seropositive protective against atopy is their an association (see 2nd column, IS' full paragraph), and that McIntire et al. further teaches that the only statistically significant data is the subgroup analysis of Caucasians and Asians who are seropositive for HAV (see table 1). The Office concluded from this that the published report by applicant in Nature confirm the examiner's validity of the statistical analysis published in the patent application. The Office maintained that the claims are broadly drawn to a screening for human's predisposition to atopy by analyzing a presence of a TIM-1 polymorphism, which requires the knowledge that a polymorphism of TIM-1 is predictive of atopy and asserted that neither the article published in Nature nor the specification provide a representative number of polymorphisms within the TIM-1 gene that are predictably associated with atopy in all populations, regardless of HAV presence or absence.

The Appellants maintain herein that they have provided statistically relevant evidence supporting a predictable correlation between the TIM-1 polymorphism in multiple populations, the validity of which was confirmed by peer review and subsequent publication in a leading journal in the art (McIntire et al.). Accordingly, the Appellants maintain that the specification provides working examples to support the pending claim element of "a method of screening for a human individual's predispositon to atopy."

With regard to the guidance and working examples provided by the specification, the Final Office Action of October 4, 2007 also asserted that "The specification does not teach the association of any polymorphism, other than 157insMTTTVP allele, in TIM-1 gene with the risk of developing atopy. The specification does not teach an association of any polymorphism with an increased likelihood of developing atopy." (page 8, line 3-6)

The Appellants submitted in their response of October 31, 2007 that they disagree with this statement, as numerous polymorphisms in TIM-1 gene and the linkage of TIM-1 gene to atopy are described in the specification on e.g. page 8, paragraph 37-38.

In response, the Office Action filed March 5, 2008 noted that the examiner agrees that not every polymorphism need to carry a predictive association with atopic disease, however a representative number of the large genus claimed need to be predictably associated with atopy.

With regard to the guidance and working examples provided by the specification, the Final Office Action of October 4, 2007 also asserted that "The specification envisions hypothetical situations where any polymorphism within the TIM-1 gene could determine the presence of atopy". (page 8, line 16-17)

The Appellants submitted in their response of October 31, 2007 that the specification teaches the use of a polymorphism in TIM-1 to determine a statistical likelihood (i.e. predisposition) of vulnerability to an atopic immunological disorder, not the presence or absence thereof. It is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 will carry predictive association with an atopic disease. One or ordinary skill in the art would be able to use the guidance and working examples taught by the specification and techniques that are well known to the art to assay statistical association of any given polymorphism with an atopy predisposition. Accordingly, the specification in view of the art provides suitable guidance and working examples so as to enable the pending claimed method.

In response, the Office Action filed March 5, 2008 agreed that neither the specification nor the claims require that every polymorphism is associated with atopy, but maintained that the claims are not limited to a specific polymorphism within the TIM-1 gene and therefore encompass any polymorphism with the TIM-1 gene. The Office further asserted that the claims are not drawn to a screening or assaying method to determine if a polymorphism is associated with atopy, but rather the claims require the knowledge of the association of a polymorphism within TIM-1 gene and atopy and the specification does not enable the skilled artisan to associate polymorphisms within the TIM-1 gene and atopy. The Office asserted that the specification provides analysis of only one, 157insMTTTVP, and demonstrates that this polymorphism is not predictably associated with atopy; therefore, that the specification does not demonstrate a single species of the large genus of polymorphisms that are predictably associated with atopy. (page 22, line 3 – 18)

The Appellants maintain herein that one or ordinary skill in the art would be able to use the guidance and working examples taught by the specification and techniques that are well known to the art to assay statistical association of any given polymorphism with an atopy predisposition. Thus, the specification provides sufficient guidance to support the pending claim element of "analyzing said individual for the presence of at least one TIM-1 polymorphism . . . wherein the presence of said polymorphism is indicative of individual's predisposition to develop atopy."

Accordingly, the Appellants maintain herein that the specification in view of the art provides suitable guidance and working examples such that one of skill in the art would be able to practice the claimed invention without undue experimentation.

The level of predictability of the art, the state of the prior art, and the level of skill in the art

With regard to the state of the art, the level of predictability in the art, and the level of skill in the art, the Final Office Action of October 4, 2007 acknowledged that the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, but states that "the level of unpredictability in associating any particular polymorphism with a phenotype is even higher." (page 9, line 2-4)

The Appellants disagreed in their response of October 31, 2007, submitting that the level of predictability with regard to the association of a TIM-1 polymorphism with an atopy phenotype is, in fact, reasonable, as evidenced by the relevant pre- and post-filing art of TIM-1 polymorphisms and the examples provided in the instant specification. For example, Chae et al (Hum Immunol. 2003 Dec;64(12):1177-82) teaches that molecular variations in the promoter and coding regions of human TIM-1 gene are associated with susceptibility to asthma in Korean population. Similarly, Graves et al. (J Allergy Clin Immunol. 2005 Sep; 116(3):650-6) teaches a 15-bp insertion/deletion in exon 4 of TIM1 being significantly related to atopy; and Gao et al (J Allergy Clin Immunol. 2005 May; 115(5):982-8) teaches data correlating genetic variation in the TIM-1 gene with asthma in African American population. Hence, polymorphisms in TIM-1 gene are predictably correlated to predisposition to develop atopy.

In response, the Office Action filed March 5, 2008 asserted that although Chae demonstrate one polymorphism is associated with asthma, Chae demonstrate that another variant, 5383_5397del was not associated (see table 1) and therefore demonstrate that not any polymorphism within TIM-1 is predictably associated with atopy. The Office further asserted that Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. The Office asserted that Noguchi et al. teach that no observation between hHAVcr-1 (TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph). Therefore, the Office concluded, the evidence in the art coupled with the evidence in the specification demonstrated the unpredictability of associating any polymorphism in the TIM- 1 gene with predisposition to developing an atopic immunological disorder in an individual. (page 22, line 21 – page 23, line 15)

The Appellants maintain herein the level of predictability with regard to the association of a TIM-1 polymorphism with an atopy phenotype in an individual, in fact, reasonably high, as evidenced

by the relevant pre- and post-filing art of TIM-1 polymorphisms (see, for example, Chae et al., Graves et al., and Gao et al.) and the examples provided in the instant specification.

With further regard to the level of predictability in the art, the Final Office Action of October 4, 2007 also asserted that "Because the claims are drawn to methods that encompass the analysis of any polymorphism of TIM-1 gene, it is relevant to note that there are multiple polymorphic positions identified in TIM-1. A Gene Card search of TIM-1 gene indicates that there are 135 SNPs of TIM-1 gene. The specification does not teach any association of these 135 polymorphisms with atopy." (page 9, lines 12-16)

The Appellants submitted in their response of October 31, 2007 that, as discussed above, techniques for generating probes with specificity for any of the TIM-1 SNPs are routine in the art, and such probes are generated by straightforward techniques as a consequence of applying the claimed method. Further, that as discussed above, the association of polymorphisms in TIM-1 gene and predisposition to atopy has been described in the specification and numerous publications.

In response to the Appellants' first point that techniques for generating probes with specificity for any TIM- 1 alleles are routine in the art, the Office Action filed March 5, 2008 agreed that the techniques for generating probes with specificity for TIM-1 alleles are routine in the art, but asserted that the claims are not drawn to a method of analyzing the TIM-1 sequence. The Office asserted that the claims are drawn to a method of diagnosis a human individual's predisposition to an atopic immunological disorder by analyzing a polymorphism for the presence of a TIM-1 polymorphism, and that as such, the claims require the knowledge of an association of polymorphism within the TIM-1 gene and atopic immunological disorders. The Office asserted that the specification does not evaluate any TIM- 1 polymorphism other than 157insMTTTVP and its association with atopic immunological disorders in an individual. (page 24, line 3 -12)

In response to the Appellants' second point that association of polymorphisms in TIM- 1 gene and predisposition to atopy have been described in the specification and numerous publications, the March 5, 2008 Office Action asserted that the prior art demonstrates the unpredictability of associating polymorphisms in TIM-1 gene with atopy as there are multiple publications that demonstrate that not all polymorphisms within TIM- 1 gene are predictably associated with atopy. Furthermore, the Office asserted that the specification does not provide a single working example of a polymorphism within TIM-1 gene that is predictably associated with atopy that is not associated with HAV seropositivity; Example 6 provides evidence of homozygous 157MTTTVP polymorphism within TIM-1 gene is predictably associated in Caucasian population that are HAV (+). (page 23, l. 15 – page 24, line 3)

The Appellants maintain herein that techniques for generating probes with specificity for any of the TIM-1 SNPs are routine in the art, and such probes are generated by straightforward techniques as a consequence of applying the claimed method. Accordingly, the method can be performed in a highly predictable manner. Further, that the association of polymorphisms in TIM-1 gene and predisposition to atopy has been described in the specification and numerous publications. Accordingly, the level of predictability of the subject methods is reasonably high.

With further regard to the level of predictability in the art, the Final Office Action of October 4, 2007 also asserted that "the prior art teaches that there are many parameter that need to be evaluated prior to using a genetic test to determine a disease and that there parameters yield gaps in information that are needed to complete a thorough screening of a genetic test." In support of this assertion, the Office Action cites Kroese et al. (Genetics in Medicine, Vol 6 (2004), p. 475-480), post filing art which the Office Action asserts teaches that since disease conditions can be multigenic and etiologies population-dependent, that genetic tests should be evaluated in terms of their detection of: 1) a particular genetic variant; 2) for a particular disease; 3) in a particular population; and 4) for a particular purpose (Kroese et al., page 477). The Examiner states that Kroese et al. further suggest that "all measures of test performance be presented with their 95% confidence intervals. (page 9, line 17 – page 10, line 7)

The Appellants submitted in their response of October 31, 2007 that the presently claimed method fulfills each of the conditions of Kroese:

1) The method as claimed teaches the detection of polymorphic sequences at a particular, well-defined genetic locus using probes for specific sequences;

2) atopic disorders are well-defined and routinely clinically reported;

3) the populations studied by the claimed method are clinically definable by the presence of disease; and

4) the specific purpose of the method as claimed, screening for a predisposition to atopy, plays to the strengths of genetic analysis precisely because the goal is association of an allele with a likelihood of disease. While discovery of the mechanistic etiology of the disease is desirable, and likely in the case of TIM-1, it is not prerequisite for the effectiveness of the method as claimed.

Furthermore, the major finding of the exemplified reduction to practice, the association of protection from atopy with the 157insMTTTVP allele in the presence of HAV seropositivity, is presented with P values representing >95% confidence. HAV+ individuals with 1 or 2, 2, or a single 157insMTTTVP allele are protected from atopy at P=0.0005, P=0.002, and P=0.004, respectively

(Table 1). The critical findings of the analyses presented in Tables S2 through S4 likewise meet this standard. As such, the recommendations of Kroese et al. are satisfied by the present Example.

In response, the Office Action of March 5, 2008 asserted that the exemplified reduction to practice does not demonstrate >95% confidence intervals for atopy and 157insMTTTVP, only for 157insMTTTVP homozygous allele in a population with HAV(+) Caucasian subjects (see table S3 and S4). The Office asserted that the specification does not teach analysis of any other polymorphism and thus does not demonstrate >95% confidence intervals for polymorphisms in the TIM-1 gene and association with atopy. (page 24, line 14-22)

The Appellants maintain herein that the major finding of the exemplified reduction to practice, the association of protection from atopy with the 157insMTTTVP allele in the presence of HAV seropositivity, is presented with P values representing >95% confidence. HAV+ individuals with 1 or 2, 2, or a single 157insMTTTVP allele are protected from atopy at P=0.0005, P=0.002, and P=0.004, respectively (Table 1). The critical findings of the analyses presented in Tables S2 through S4 likewise meet this standard. As such, the recommendations of Kroese et al. are satisfied by the present Example, providing support for the Appellants' arguments of the high predictability of the pending method.

With further regard to the level of predictability in the art, the Final Office Action of October 4, 2007 also cited Lucentini (The Scientist, 2004, Vol 18, page 20), which it allegedly teaches that "it is strikingly common for follow-up studies to find gene-disease associations wrong." (page 10, line 12-13)

The Appellants noted in their response of October 31, 2007 that Lucentini in the second column, first full paragraph, teaches recommendations for avoiding this error: first, accounting for "prior probability", a subjective but reasonable measure of how plausible the gene-disease association in question looked prior to the study; and second, including a large enough sample size to avoid a cofounder population stratification effect.

The Appellants submitted that the presently claimed method fulfills both of these conditions: First, as reviewed above, the importance of the TIM-1 gene family is described in the specification, which includes numerous referenced publications linking the TIM genes to multiple immune-mediated diseases and description of the important role of the receptor encoded by the TIM-1 gene in immunological responses. The specification further states in the introduction to Example 6, page 53, paragraph 193:

> TIM-1 is expressed by activated CD4 T cells during the development of helper T cell (Th2) responses and appears to regulate cytokine production. Therefore, we postulated that HAV interaction with TIM-1 on lymphocytes could modify T cells in a

> manner that protects against atopy, and that polymorphisms in TIM-1 might alter susceptibility to atopy.

The introduction further states:

> By sequencing lymphocyte cDNA, we identified a six amino acid insertion, 157insMTTTVP. 157insMTTTVP is located at the center of an extracellular mucin-like region that is required for efficient HAV uncoating, and because 157insMTTTVP lengthens this critical region by 12-14%, this variation may impact the efficiency of viral entry.

As such, the prior probability of gene-disease association was reasonably considered to be high in the course of designing the experiment.

Second, the population stratification effect results from the tendency of populations to carry high frequencies of both certain genes and certain diseases owing to common ancestry. As reviewed above, the purpose of the method as claimed is screening for a predisposition to atopy, not discovery of a causal link of polymorphism to disease. While discovery of the mechanistic etiology of the disease is desirable, and likely in the case of TIM-1, it is not prerequisite for the effectiveness of the method as claimed; genetic linkage alone is sufficient. Moreover, since the population displaying atopic conditions is large and diverse as evidenced in the present specification, the likelihood of founder effects is small, and the likelihood of such effects reducing the informativity of the data in a study comprising multiple ethnic groups is smaller.

Accordingly, the Appellants submitted that the recommendations of Lucentini are satisfied with respect to the instant application, substantiating the reliability of the exemplified results and demonstrating that the relevant art is not highly unpredictable.

In response, the Office Action of March 5, 2008 asserted that although the population is large and diverse that is presented in the specification, the data presented in the subpopulation findings in the specification demonstrates that unpredictability of associating a polymorphism with atopic immunological disorder in any population. The Office asserted that the critical findings demonstrated in table S3 and S4 demonstrate that the polymorphism is not associated with atopic immunological disorder in every population, as both Caucasians and Asians that are not HAV(+) who carry either the homozygous or heterozygous allele 157insMTTTVP; furthermore the specification does not demonstrate a population of individuals with the 157insMTTTVP and their predisposition to develop atopy. The Office asserted that the specification demonstrates that the recommendations of Lucentini suggesting a large, more diverse sample size is necessary to demonstrate an association with a gene and disorder, as the large study presented in the specification demonstrates that subpopulations, those that are HAV negative and different ethnic

groups, will not have a protection against developing atopy with the presence of the polymorphism 157insMTTTVP. (page 25, line 1-18)

The Appellants maintain herein that the examples provided do meet the criteria set forth by Lucenti, namely, accounting for "prior probability" and including a large enough sample size to avoid a cofounder population stratification effect, and thus, that there is no reason to doubt the predictability of the gene-disease associations they have provided.

With further regard to the level of predictability in the art, the Final Office Action of October 4, 2007 asserted that the post-filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy. To support these assertions, the Office Action cited Noguchi et al. (Genes and Immunity (2003) 4: 170-173) as teaching a lack of association between TIM-1 gene polymorphisms and asthma in Japanese asthmatic families. (page 11, line 3-13)

The Appellants noted in their response of October 31, 2007 that none of the polymorphisms identified by Noguchi et al. were associated with asthma in the present experimental examples (specification, Example 6; Noguchi et al., page 170, right column, second full paragraph).

Appellants additionally noted that the instant Example 6 was practiced upon individuals answering to calls for allergic reactions and responding positively for allergic rhinitis, atopic dermatitis and food allergy, and positive for specific IgE against local allergens, not for familial asthma (specification, page 57, paragraph 201). These are separate conditions. As such, there is no apparent contradiction between the results of Noguchi et al. and those of the present example.

Moreover, Appellants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

In response, the Office Action of March 5, 2008 noted that the claims are drawn to the presence of analyzing a polymorphism within the TIM- 1 gene and the presence of a polymorphism is indicative of developing atopic immunological disorder. The Office asserted that the claims are drawn to atopy, which encompasses asthma including familial asthma and are drawn to the association of any polymorphism with the TIM- 1, which encompasses the polymorphisms taught by Noguchi. The Office noted that claim 1 and 7 recite "at least one TIM-1 polymorphism" and therefore encompass any polymorphism within the TIM-1 gene. The Office asserted that Noguchi et al. demonstrates the unpredictability of associating any polymorphism in the TIM-1 with atopic immunological disorder, that Noguchi et al. demonstrates polymorphisms in TIM- 1 are not

associated with asthma and further demonstrates that different populations are needed to elucidate the role of TIM- 1 polymorphisms in atopic diseases (see pg. 172, 2nd column, last paragraph), and concluded from this that Noguchi et al. demonstrates that some polymorphism within TIM-1 are not associated with atopy, such as asthma. (page 26, line 2-17)

The Appellants maintain that instant Example 6 demonstrates a correlation between TIM-1 gene polymorphism and allergic rhinitis, atopic dermatitis and food allergy, and positive for specific IgE against local allergens, not for familial asthma (specification, page 57, paragraph 201). As such, there is no apparent contradiction between the results of Noguchi et al. and those of the present example. Further, the Appellants maintain that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

To support the Office Action's assertions that the post-filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy, the Office also cited the Appellants' own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), as teaching that only individuals that are HAV positive are predictably correlative to protection against atopy in individuals that have the polymorphic insertion in TIM-1 gene. (page 11, l. 14 - page 15, line 3)

The Appellants noted in their response of October 31, 2007 that these results are, in fact, confirmatory of those presented in the instant application, namely, that serotype HAV+ insertion allele carriers are protected against atopy while HAV- carriers are not. As such, there is no apparent contradiction between the result of Umetsu et al. and those of the present examples. The Appellants also emphasized at that time that it is nowhere recited or implied in the instant application that every polymorphism of TIM-1 will carry association with an atopic disease in the absence of any other infectious agent or associated gene. Appellants submit that there is no *a priori* reason that viral infection should be excluded from the characteristics of an individual suffering from atopy in whom the method finds use.

In response, the Office Action of March 5, 2008 asserted that Umetsu provides evidence that individuals that are HAV negative are not associated with atopy (see pg. 92, 1st full paragraph). The Office asserted that the claims are drawn to diagnosing any human for atopy by detecting the presence of a polymorphism in TIM-1. The Office asserted that Claims 1, 4 , 7, 20 and 23 are not limited to the population being HAV+ or - and the specification demonstrates the unpredictability of associating any population with any polymorphism with atopy and Umetsu et al. provides further

evidence of the unpredictability of associating any individual with atopy. With regard to Appellants' assertion that there is no a priori reason that viral infection should be excluded from individuals suffering atopy, the Office asserted that in the instant case, the presence of HAV is the only population demonstrated in the specification to be associated with atopy and 157insMTTTVP polymorphism. Furthermore, the Office asserted that although the claims do not require that every polymorphism is associated with atopy, the claims recite "at least one TIM- 1 polymorphism" and thus are not limited to specific polymorphisms and therefore broadly encompass any polymorphism within TIM- 1 gene. (page 27, line 1-13)

The Appellants maintain that the results of Umetsu et al. are, in fact, confirmatory of those presented in the instant application, namely, that serotype HAV+ insertion allele carriers are protected against atopy while HAV- carriers are not. Further, that it is nowhere recited or implied in the instant application that every polymorphism of TIM-1 will carry association with an atopic disease in the absence of any other infectious agent or associated gene. Appellants submit that there is no *a priori* reason that viral infection should be excluded from the characteristics of an individual suffering from atopy in whom the method finds use.

To further support the Office Action's assertions that the post-filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy, the Office also cited Graves et al. (J Allerg Clin Immunol. 2005, vol 1 18, pages 650-656) as teaching that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. (page 12, line 4 – 16)

The Appellants noted in their response of October 31, 2007 that none of the polymorphisms identified as not significantly associated with atopy by Graves et al. were found to be associated with atopy in the present experimental examples (specification, Example 6; Graves et al., page 170, right column, second full paragraph). Moreover, Appellants emphasized that it is nowhere recited or implied in the instant Application that <u>every</u> polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

The Appellants submitted that, as such, there is no apparent contradiction, and indeed, given the differing polymorphisms assessed, there is significant consonance between the results of Graves et al. and those of the present example. Graves et al. find that multiple alleles show statistically significant association with atopic conditions (Graves et al., page 652, right column, second full paragraph). Graves et al. teach that these "associations were strong enough to remain

significant after adjustment for multiple comparisons" (transition paragraph from page 653-654). Contra the Examiner, Graves et al. teach that although a limitation of the analysis is reflected in the ethnic heterogeneity of the Tucson population, similar results were replicated in children with two Caucasian parents, indicating that the significant associations are unlikely to be related to population stratification as the result of ethnicity (page 655, right column, third full paragraph). Accordingly, the study does not cast doubt upon but rather substantiates the rationale and feasibility of the claimed method.

Moreover, Gao et al. (*supra*) report that genetic variants of the TIM-1 gene contribute to asthma susceptibility in the African-American population. In Gao et al., frequencies of the TT genotype for a single nucleotide polymorphism rs2277025 and a homozygous deletion variant 157delMTTTVP in the fourth exon of the TIM-1 gene were higher among patients with patients with asthma compared with controls (odds ratio [OR], 2.779, P = .016; and OR, 3.09, P = .022, respectively). The association was further substantiated by haplotype analysis of these and two additional SNPs (OR, 2.48; P = .004), and also by family-based tests for the allele and haplotype carrying 157delMTTTVP (P = .009 and P = .048, respectively). Accordingly, TIM-1 allelic variation has been statistically associated with atopic conditions in an African American population.

Similarly, the Appellants submitted in their response of October 31, 2007 that the level of skill in the art is also relatively high, noting that the relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing nucleic acid-based assays is high. It would therefore be straightforward for one of skill in the relevant art to distinguish TIM-1 alleles which are of use in the presently claimed method.

With regard to the Appellants' first point, the Office Action of March 5, 2008 maintained that claim 1 and 7 are broadly drawn to "at least one TIM1 polymorphism" and are not limited to specific polymorphisms and therefore the claims are broadly drawn to "any" polymorphisms within TIM-1 gene, which encompasses the polymorphisms studied by Graves et al. The Office also maintained that Graves et al. demonstrates that polymorphisms within TIM 1 gene are not predictably associated with atopy. (page 27, line 14-22)

With regard to the Appellants' second point that the study does not cast doubt upon but rather substantiates the rationale and feasibility of the claimed method, the March 5, 2008 Office Action asserted that Graves et al. teaches that their findings need to be replicated in other studies (see page 655, 1st column, last paragraph), which demonstrates their doubt on the results of the

study and does not substantiate the rationale or feasibility of the claimed method. Furthermore, the Office asserted that Graves et al. teach several different polymorphisms within TIM-1 gene that were not statistically relevant and not associated with atopy (see table E2) and further demonstrate that the 15bp deletion of the TIM-1 gene (see pg. 655, 1st column, 1st paragraph) was not associated with asthma but was associated with atopic dermatitis, which demonstrates the unpredictability of any atopy immunological disease and a polymorphism within the TIM-1 gene. Therefore, the Office concluded, Graves et al. demonstrates the unpredictability of associating any polymorphism within TIM 1 gene with atopic immunological disorder. (page 28, line 1-15)

With regard to the Appellants' third point that Gao et al. demonstrates TIM-1 allelic variation is statistically associated with atopic conditions in African American populations, the March 5, 2008 Office Action asserted that Gao et al. demonstrate that African Americans that do not have the MTTTVP (see table II and pg. 987, 1st column, last paragraph) insertion are predictability associated with asthma which is the opposite of the claimed method. The Office asserted that the claims are drawn to the presence of a polymorphism that is associated with an individual predisposition to atopic immunological disorder (claim 1) and further limited to detecting the presence of MTTTVP; therefore the claims are drawn to associating the insertion of MTTTVP with predisposition to atopic immunological disorder, whereas the teaching of Gao et al. teach that the deletion, not insertion of MTTTVP is associated with African American population and asthma (see pg. 987, 1 st column, last paragraph). Furthermore, the Office asserted, Gao et al. demonstrate that the HAV seronegative population and the insertion variant is marginally associated with asthma (see pg. 985, 2nd column, last paragraph), which demonstrates the polymorphism is not statistically associated with atopy. Therefore, the Office concluded, Gao et al. provides evidence of the unpredictably of associating a polymorphism within TIM1 with atopic immunological disorder. (page 28, line 16 – page 29, line 10)

The Appellants maintain herein that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition. The Appellants have provided examples in the specification and in the art, for example, Guo et al., that are highly correlative, and thus, the level of predictability in the art is reasonably high. The skill level of those developing and using methods for manipulating DNA and performing nucleic acid-based assays is high. Finally, the level of skill in the art is such that it would be straightforward for one of skill in the relevant art to distinguish TIM-1 alleles which are of use in the presently claimed method.

Accordingly, the Appellants maintain that the state of the relevant art is sufficiently well-developed, the level of predictability in the relevant art is sufficiently high, and the level of skill in the relevant art is sufficiently high that one of skill in the art would be able to practice the claimed invention without undue experimentation.

Quantity of experimentation

With regard to the quantity of experimentation that would be required of the ordinary skilled artisan, the Final Office Action of October 4, 2007 asserted that "Given the lack of guidance in the specification with regard to association of any polymorphism in the TIM-1 gene with any atopic immunological disorder in any individual along with the evidence in the art that demonstrates that not every polymorphism of TIM-1 gene is associated with an immunological disorder, the quantity of experimentation in this area is extremely large" (page 13, line 13-17)

The Appellants noted in their response of October 31, 2007 that the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]
As the court explained[4]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

The Appellants submitted that practitioners in the chemical and molecular biological arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[5]

The Appellants submitted that the claims recite a method of screening for a human individual's predisposition to atopy, the method including analyzing the individual for the presence of

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[3] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

[4] *In re Wands* 8 USPQ 2d at 1404

[5] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

at least one TIM-1 polymorphism by contacting a biological sample including genomic DNA, mRNA or transcript thereof from an individual with probes that specifically bind under stringent conditions to the nucleic acid sequence of a TIM-1 allele, where the presence of the polymorphism is indicative of an individual's predisposition to develop atopy.

The Appellants submitted that the only experiments that need be performed to enable the entire scope of the claim are those designed to assess the association of a TIM-1 polymorphism with an atopic condition in a population of interest. The sequence of such a polymorphism is determined through routine experimentation, typically employing nothing more than performing the same assay disclosed in the specification on a clinically defined cohort using polypeptides made by routine, high-throughput sequencing and DNA synthesis techniques. Since these experiments are routine in the art, no undue experimentation is required. In other words, the only experimentation required to enable the claimed invention are experiments to confirm a statistical association of an allele in a population, and since this only requires a routine assay to determine, no undue experimentation is necessary.

In sum, the amount of experimentation required to establish conditions in which detection of a polymorphism in the TIM-1 gene permits the screening for a predisposition to atopy would not be undue because a) a working example has been provided, b) guidance on how to assess the association has been provided, c) it is straightforward to establish a reasonable correlation between atopy and members of the species within a genus of this breadth, and d) one of skill in the art would be able to perform such screening experiments as a matter of routine.

In response, the Office Action of March 5, 2008 maintained that, while identifying polymorphic allelic variants of a gene is routine in the art, the ability to predictably correlate the polymorphic variants with a disease is unpredictable. The Office noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 17 14 (BPAI 1991). Therefore, the Office concluded, considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in unpredictable, excessive and undue amount of experimentation to exercise the invention as claimed.

The Appellants maintain herein that ample guidance and working examples to make and use the presently claimed invention is provided in the specification and such experiments are routine in the art. Furthermore, the state of the relevant art is sufficiently well developed, the level of predictability in the relevant art is sufficiently high, and the level skill in the art is sufficiently high. Accordingly, no undue experimentation would be required of the ordinary skilled artisan.

Thus, the Appellants maintain that the nature of the invention is reasonably simple, the claims are not unduly broad, the specification provides suitable guidance and working examples, the state of the art at the time of the present invention was sufficiently well-developed and the level of predictability in the art at the time of the present invention was sufficiently high that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Consequently, the Appellants contend that the present claims meet the requirements of 35 U.S.C. § 112, first paragraph, with respect to enablement, and request that this rejection be withdrawn.

II. Claims 1, 4, 7 and 23 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

The Final Office Actions of October 4, 2007, the Office Action of March 5, 2008 and the Final Office Action of October 29, 2008 assert that the claims are broadly drawn to methods for diagnosing predisposition to any atopic immunological disorder comprising determining any polymorphism in any human individual (claim 1). Further, it is asserted that the claims are broadly drawn to methods comprising the detection of a variety of nucleic acids, including any polymorphic variant of TIM-1 gene that is associated with any type of atopy. The Appellants respectfully disagree with the examiner.

The Appellants have submitted previously and maintain herein that the claims are drawn to methods of screening individual's for disposition to atopy. Atopy is a well characterized with underlying immune dysfunction which manifests in specific clinical phenomenon. The art refers to this condition in multiple references provided herein.

Furthermore, the Appellants have submitted previously (see the Responses to Office Actions dated October 31, 2007 and August 5, 2008) and maintain herein that they have unambiguously proven the link between TIM-1 and atopy (see working examples). The sequence of TIM-1 and related genes in the TIM family is provided in the specification (see sequence listing). A description of common polymorphisms in TIM-1 and the linkage of TIM-1 locus to development of atopy can be found in the specification on e.g., Page 8, paragraph 37-43; page 13, paragraph 51; page 46, paragraph 169-175. Methods for detecting polymorphisms in a gene (page 14, paragraph 56) and

methods for performing statistical analysis to assess whether a polymorphism in TIM-1 is linked to atopy is described in the specification (see Materials and methods, page 57, paragraphs 201-204).

While there may be sequences within the genus defined by "TIM-1 polymorphism" which will not significantly associate with atopy, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work. The court has very clearly explained[6]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

The claims of the instant application encompass a method of screening for a human individual's predisposition to atopy which includes analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample including DNA or mRNA from the individual with probes that specifically bind under stringent conditions to the nucleic acid sequences of TIM-1, where the presence of the polymorphism is indicative of an individual's predisposition to develop atopy. Since one of skill in the art would recognize that a reasonable correlation between atopy and members of this genus is readily established by the disclosure of the instant application, and since every species in a genus does not have to be tested for the genus to be enabled, extensive, per-sequence disclosure or guidance regarding the active species in the genus does not have to be provided in order for a genus of this scope to be enabled.

As such, the Appellants maintain that the specification provides adequate written description of claimed methods.

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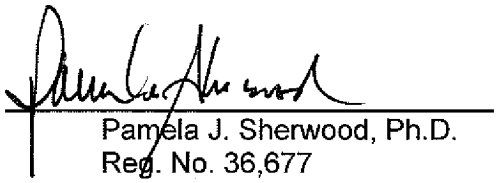
[6] *In re Angstadt*, 190 USPQ 214, at 219 (CCPA 1976)

In view of the arguments set forth above, the Appellants respectfully request that the rejection of Claims 1, 4, 7-8 and 20-23 under 35 U.S.C. 112, first paragraph for enablement and of Claims 1, 4, 7 and 23 under 35 U.S.C. 112, first paragraph for written description be withdrawn, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

The appropriate fee is either attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-0815.**

Respectfully submitted,
BOZICEVIC, FIELD AND FRANCIS LLP

Date: April 13, 2009



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VIII. CLAIMS APPENDIX

The claims on appeal are as follows:

1. (previously presented) A method of screening for a human individual's predisposition to atopy, the method comprising:

analyzing said individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample comprising DNA or mRNA from said individual with probes that specifically bind under stringent conditions to nucleic acid sequences of a TIM-1 gene;

wherein the presence of said polymorphism is indicative of an individual's predisposition to develop said atopy.

2. (withdrawn)

3. (withdrawn)

4. (previously presented) The method according to Claim 1, wherein said analyzing step comprises contacting a biological sample comprising DNA or mRNA from said individual with a probe that specifically binds to the nucleic acid sequence ATGACAACGACTGTTCCA, SEQ ID NO:22, BASES 472-489, encoding the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163; and

detecting the presence of a complex formed between said probe and said DNA or mRNA.

5-6. (canceled)

7. (original) The method according to Claim 1, wherein said biological sample is blood or a derivative thereof.

8. (previously presented) A method of screening for a human individual's predisposition to atopy, the method comprising:

analyzing said individual for the presence of an INS157 polymorphism in TIM-1 by contacting a biological sample comprising DNA or mRNA from such individual with a probe that specifically binds to the nucleic acid sequence ATGACAACGACTGTTCCA, SEQ ID NO:22, bases 472-489, encoding the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163;

detecting the presence of a complex formed between said probe and said genomic DNA, mRNA or a transcript thereof; and

analyzing said individual for the presence of hepatitis A virus (HAV) seropositivity wherein said seropositivity in an individual comprising an allele of TIM-1 comprising the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 is indicative of a reduced risk of developing atopy.

9-19. (canceled)

20. (previously presented) A method of screening for a human individual's predisposition to atopy, the method comprising:

analyzing said individual for the presence of an INS157 polymorphism in TIM-1 by contacting a biological sample comprising DNA or mRNA from said individual with a probe that specifically binds to a nucleic acid sequence encoding the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163;

wherein the presence of said INS157 polymorphism is indicative of an individual's predisposition to develop said atopy.

21. (previously presented) The method according to Claim 20, wherein said biological sample is blood or a derivative thereof.

22. (previously presented) The method according to Claim 20, further comprising the step of:

analyzing said individual for the presence of hepatitis A virus (HAV) seropositivity,

wherein seropositivity in an individual expressing an allele of TIM-1 comprising the amino acid sequence MTTTVP, SEQ ID NO:25, residues 158-163 is indicative of a reduced risk of developing atopy.

23. (previously presented) A method of screening for a human individual's predisposition to atopy, the method comprising:

analyzing said individual for the presence of at least one TIM-1 polymorphism in exon 3 by contacting a biological sample comprising DNA or mRNA from said individual with probes that specifically bind under stringent conditions to nucleic acid sequences in exon 3 of a TIM-1 gene;

wherein the presence of said polymorphism is indicative of an individual's predisposition to develop said atopy.

IX. EVIDENCE APPENDIX

The following references were cited in the Arguments above. All have been provided during the course of prosecution.

Sizing et al. (2007) J. Immunol. 178(4):2249-61

Graves et al. (2005) J Allergy Clin Immunol. 116(3):650-6

McIntire et al. (2003) Nature. 425: 576

Chae et al (2003) Hum Immunol. 64(12):1177-82

Graves et al. (2005) J Allergy Clin Immunol. 116(3):650-6

Gao et al (2005) J Allergy Clin Immunol. 115(5):982-8

Kroese et al. (2004) Genetics in Medicine 6:475-480

Lucentini (2004) The Scientist 18:20

Noguchi et al. (2003) Genes and Immunity 4: 170-173

Umetsu et al. (2004) Ann NY Acad Sci 1029:88-93

X. RELATED PROCEEDINGS APPENDIX

none